2019-nCoV Literature Situation Report (Lit Rep)
February 12, 2020

Key Takeaways

➢ **2019-nCoV Case Fatality Rates have a broad range, depending on age, severity of illness at time of diagnosis, and sex. A calculated CFR for hospitalized patients ranges from 0.7% for those presenting with mild illness 9.5% for patients with two of three risks mentioned.**

➢ **The importance of contact tracing, screening, and other public health control measures has been emphasized in recent models considering that some infected patients may infect more secondary cases than others.**

➢ **Sputum specimens appear to be the most accurate specimen type for laboratory diagnosis of 2019-nCoV, with BALF specimens considered very accurate only for severe cases.**

➢ **The importance of planning for limited healthcare resources during a local or regional 2019-nCoV epidemic is highlighted.**

Transmission and Global Spread

- A review of all 2019-nCoV patients reported to the Chinese Center for Disease Control and Prevention (Chinese CDC) up to 26 January, 2020 was undertaken to describe the affected populations and to estimate severity and transmissibility.
- Of 8866 patients, 4021 (45%) were laboratory confirmed.
    - Ages were similar between confirmed and suspect cases (49 years; SD, $\pm$16 yrs). Fourteen of the 4021 confirmed cases were in children <10 years old. Most confirmed cases were 30-65 years of age.
    - Wuhan patients were on average older and more likely to be male compared to elsewhere in China.
    - Among confirmed cases, median time from symptom onset to diagnosis was 5 days. Mild pneumonia (70%) was most often seen at time of diagnosis, with about 26% diagnosed with severe pneumonia and 5% with no evidence of pneumonia.
    - Incidence shifted from sporadic to exponential on 1 January. Starting 17 January, more confirmed patients were reported outside of Wuhan than in Wuhan.
- Bias-adjusted Case Fatality Rate (CFR) estimates:
    - Among confirmed cases, calculated CFRs were higher than observed CFRs (3.1% and 1.4%, respectively).
    - Ranged from 0.7% for those with mild disease at time of diagnosis to 9.5% for patients with two of three risks (male, $\geq$60 years of age, or severe disease at diagnosis)
    - Were higher in patients $\geq$60 years of age (5.3% vs. 1.4% <60 yrs), patients with longer time from onset to diagnosis (3.1%, >5 days vs. 1.3%, $\leq$5), and among males (4.5% vs. 1.3%)
- R_0 estimates were highest (R_0, 3.2-4.8) for long incubation (6.4 days) and infectious (9.2 days) periods; and lowest (R_0, 2.2-2.8) for short incubation (3.8 days) and infectious (5.2 days) periods, with added variability due to reporting rate(30%-100%).

Yang Y, et al (Feb 11, 2020) Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. BMJ. Pre-print accessed Feb 12 from https://www.medrxiv.org/content/10.1101/2020.02.10.20021675v1

- A gastrointestinal route of infection is proposed by Liang, et al., based on ACE2 [host cell receptor] mRNA expression in healthy human small intestines and other molecular evidence for biologic plausibility.
- It is hypothesized that eating 2019-nCoV-infected wild animals could result in human infection; and diarrhea as a 2019-nCoV symptom could both indicate a GI route of transmission and be risk for on-going transmission.
  Liang W, et al (Feb 11, 2020) Diarrhea may be underestimated: a missing link in 2019 novel coronavirus. BMJ. Pre-print accessed Feb 12 from https://www.medrxiv.org/content/10.1101/2020.02.03.20020289v1

- A case series of 67 2019-nCoV pneumonia patients (NCP) was evaluated to assess possible 2019-nCoV transmission from aerosol contact with the conjunctiva. A conjunctival swab sample from one patient with no ocular symptoms was RT-PCR positive; one patient with conjunctivitis was RT-PCR negative. [*Note:* The weak study design did not address their hypothesis, but the lab findings are potentially of interest.]
  Zhou Y, et al (Feb 12, 2020) Ophthalmologic evidence against the interpersonal transmission of 2019 novel coronavirus through conjunctiva. BMJ. Pre-print accessed Feb 12 from https://www.medrxiv.org/content/10.1101/2020.02.11.20021956v1

Modelling and Prediction

- Hebert-Dufrense, *et al.* apply network theory to improve basic estimates of R_0, using added information from the *numeric heterogeneity of secondary infections* – that is, the fact that some individuals create more secondary infections then others.
- A range of predictions for the final size of the Wuhan 2019-nCoV epidemic is provided, using R_0 estimates from early cases and SARS data for the underlying distribution of secondary cases. The resulting range, as a fraction of the total susceptible population, is 5%-40%.
- With a **high heterogeneity (**e.g., transmission mostly maintained by "super-spreading" events), the epidemic is less likely to spread extensively and be easier to manage with contact tracing, screening and infection control
- With **low heterogeneity**, containment strategies will likely fail, and pandemic of 2019-nCoV is likely.
- Overall, this network modeling approach highlights the need for contact tracing during emerging infectious disease outbreaks; and the need to look beyond R_0 when predicting epidemic size.
  Hebert-Dufrense L, et al. (Feb 11, 2020) Beyond R0: the importance of contact tracing when predicting epidemics. BMJ. PRE-PRINT. Accessed Feb 12 from https://www.medrxiv.org/content/10.1101/2020.02.10.20021725v1

- The upper bound for basic reproduction number, R, in the current US context is estimated based on the number of imported primary cases and secondary cases, and using a maximum likelihood technique. R is found to be less than 1 (subcritical) at this time. Depending on the value of a dispersion parameter reflecting heterogeneity of spread [see above], 2-9 secondary cases from 10 imported cases would be required for R to exceed 1.

Blumberg S, et al (Feb 11, 2020) Assessing the plausibility of subcritical transmission of 2019-nCoV in the United States. BMJ. PRE-PRINT. Accessed Feb 12 from
https://www.medrxiv.org/content/10.1101/2020.02.08.20021311v1

Clinical Outcomes and Access to Care

- A case series of nine pregnant women with COVID-2019 provides a description of clinical characteristics and initial information on risk of vertical transmission.
- None of the patients developed severe COVID-19 pneumonia or died, as of Feb 4, 2020.
  - Seven patients presented with a fever; four, with cough; three, myalgia; and two, sore throat or malaise. Five had lymphopenia (<1·0 × 10^9 cells per L); three, increased aminotransferase concentrations. Fetal distress was monitored in two cases.
- All nine patients had a caesarean section (third trimester) leading to a livebirth.
- All nine newborns had a 1-min Apgar score of 8–9 and a 5-min Apgar score of 9–10.
- Six patients had amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples tested for SARS-CoV-2. All samples tested negative for the virus.

  Chen H, et al. (Feb 12, 2020) Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. The Lancet. https://doi.org/10.1016/S0140-6736(20)30360-3

- Shang, *et al.* respond to an earlier article by Russell, *et al.* on clinical evidence of corticosteroid therapy in severe coronavirus infections. Shang, *et al.* describe the potential for selection bias and confounding in observational studies, given that usually only critically ill patients are treated with corticosteroid therapy. They further note that four references in the original articles cited as having "conclusive data…indicating harm" were not definitive, and that Russell, *et al.* did not address 25 other inconclusive studies. Additional studies supporting low-moderate dose corticosteroid therapy for severely ill coronavirus and influenza patients are cited.
- An expert consensus statement from the Chinese Thoracic Society identifies basic principles for corticosteroids use, including that corticosteroids can be used prudently in critically ill COVID-2019 patients, with special caution for patients with hypoxaemia due to underlying diseases or who regularly use corticosteroids for chronic diseases; that dosage should be low-to-moderate (≤0·5–1 mg/kg per day methylprednisolone or equivalent); and that duration should be short (≤7 days).

  Shang L, et al. (Feb 11, 2020) On the use of corticosteroids for 2019-nCoV pneumonia. The Lancet. https://doi.org/10.1016/S0140-6736(20)30361-5

- A case series of 17 COVID-2019 cases from Dazhou, China is described. In comparing discharged and non-discharged patients, the authors find that younger age and higher lymphocytes and monocyte levels may be factors in faster recover.

  Li J, et al (Feb 12, 2020) Epidemiological and Clinical Characteristics of 17 Hospitalized Patients with 2019 Novel Coronavirus Infections Outside Wuhan, China. BMJ. PRE-PRINT. Accessed Feb 12 from https://www.medrxiv.org/content/10.1101/2020.02.11.20022053v1

Testing and Treatment

- The diagnostic accuracy of different respiratory specimens for 2019-nCoV detection is assessed by Yang, *et al*.

- Specimens were collected from confirmed novel coronavirus pneumonia (NCP; severe or mild) patients in a Guangdong, China hospital; and tested using the Qiagen QIAamp RNA Viral Kit and a Chinese Food & Drug Administration-approved, quantitative RT-PCR 2019-nCoV detection kit.
- 866 specimens from 213 hospitalized patients were tested, including nasal swabs (n=490), throat swabs (n=205), sputum (n=142) and bronchoalveolar lavage fluid (BALF; n=29). Sample collection was grouped by days after symptom onset (0-7 days, 8-14 days, and >14 days).
- <u>Overall, sputum was found to be the most accurate specimen type for laboratory diagnosis of NCP.</u>
    - Sputum specimens taken with 14 days after onset were positive in 74-89% of cases (mild and severe). From 15 days onward, 43-61% continued to test positive.
    - Nasal swab specimens taken within 14 days after onset were positive in 54-73% of cases, dropping to 50-55% after 14 days.
    - Throat specimens taken within 7 days were positive in 60-61% of cases. From 8 days onward, this dropped to 37%-50% of severe cases and 11%-30% of mild cases.
- Among 10 severe cases, positive BALF specimens were found from 6-23 days after onset; and 100% tested BALF-positive at 8-14 days after symptom onset. Three mild cases were BALF-negative.
- Among 13 NCP cases with specimens from upper (throat, nasal, sputum) and lower respiratory (BALF) samples across multiple time periods, viral RNA was reliably detected in the lower respiratory tract of cases of severe NCP cases, but not in upper respiratory samples.
    - *Yang Y, et al (Feb 12, 2020) Laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. BMJ. PRE-PRINT. Accessed Feb 12 from* https://www.medrxiv.org/content/10.1101/2020.02.11.20021493v1

Policy and Prevention

- A national survey of primary care providers in China to assess 2019-nCoV prevention practices had a 62% response rate. Most respondents were proactively studying 2019-nCoV (99%); and guiding patients on preventive measures (94%). While only 48% were referring patients meeting a suspect case definition [undefined here] to hospitals for further diagnosis and treatment, this response varied significantly by geographic region, specialty, and practice setting.
    - *Xu Z, et al (Feb 12, 2020) Primary Care Practitioners' Response to 2019 Novel Coronavirus Outbreak in China. Pre-print access Feb 12 from* https://www.medrxiv.org/content/10.1101/2020.02.11.20022095v1

- Zhang describes the challenges early in the Wuhan 2019-nCoV outbreak. Areas mentioned with implications for policy include transparency of information, including timely public information; provider awareness of atypical presentations, potentially affecting spread across provider settings and insufficient use of respiratory precautions by providers; appreciation of alternate, non-respiratory routes of transmission; availability of personal protective equipment; assuring therapeutic drug supply; and implications of insufficient hospital beds and cancellation of outpatient services, ultimately impacting disease spread, morbidity, and mortality.
    - *Zhang H (Feb 11, 2020) Early lessons from the frontline of the 2019-nCoV outbreak. The Lancet.* https://doi.org/10.1016/S0140-6736(20)30356-1

- Given that limited healthcare resources have become a serious bottleneck to the Wuhan epidemic response, an SEIR modeling approach was combined with a healthcare-resource-adjusted vulnerability index to inform public health planning for constrained healthcare resources in this epidemic response.

- In addition to identifying vulnerabilities across 100 cities in China, the framework provided integrates human movements and healthcare resources data in a way that could also be more generally useful.

  Zhou H, et al (Feb 12, 2020) Healthcare-resource-adjusted vulnerabilities towards the 2019-nCoV epidemic across China. PRE-PRINT. Accessed Feb 12 from https://www.medrxiv.org/content/10.1101/2020.02.11.20022111v1

Other Resources
- [ClinicalTrials.gov has a list of 23 trials related to 2019-nCoV.](#)
- [Repository of disaster management recommendations and guidance from PH agencies.](#)
- [Red Book chapter on coronaviruses which covers SARS and MERS. Source is American Academy of Pediatrics](#)
- [Genome Typing Tool – Genome Detective](#)

In addition to the articles described here, there are numerous editorials, commentaries, and technical papers available to view via the [2019-nCoV SharePoint site](#) along with previous Lit Reps.